Cardiorenal Syndrome in the Hospital

Wendy McCallum and Mark J. Sarnak

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 10/16/2024

Abstract

The cardiorenal syndrome refers to a group of complex, bidirectional pathophysiological pathways involving dysfunction in both the heart and kidney. Upward of 60% of patients admitted for acute decompensated heart failure have CKD, as defined by an eGFR of <60 ml/min per 1.73 m². CKD, in turn, is one of the strongest risk factors for mortality and cardiovascular events in acute decompensated heart failure. Although not well understood, the mechanisms in the cardiorenal syndrome include venous congestion, arterial underfilling, neurohormonal activation, inflammation, and endothelial dysfunction. Arterial underfilling may lead to activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, leading to sodium reabsorption and vasoconstriction. Venous congestion likely also mediates and perpetuates these maladaptive pathways. To rule out intrinsic kidney disease that is distinct from the cardiorenal syndrome, one should obtain a careful history, review longitudinal eGFR trends, assess albuminuria and proteinuria, and review the urine sediment and kidney imaging. The hallmark of the cardiorenal syndrome is intense sodium avidity and diuretic resistance, often requiring a combination of diuretics with varying pharmacological targets, and monitoring of urinary response to guide escalations in therapy. Invasive means of decongestion may be required including ultrafiltration or KRT such as peritoneal dialysis, which is often better tolerated from a hemodynamic perspective than intermittent hemodialysis. Strategies for increasing forward perfusion in states of low cardiac output and cardiogenic shock may include afterload reduction and inotropes and, in the most severe cases, mechanical circulatory support devices, many of which have kidney-specific considerations.

CJASN 18: 933–945, 2023. doi: https://doi.org/10.2215/CJN.0000000000000064

Division of Nephrology, Tufts Medical Center, Boston, Massachusetts

Correspondence: Dr. Mark J. Sarnak, Division of Nephrology, Tufts Medical Center, Box 391, 800 Washington Street, Boston, MA 02111. Email: msarnak@tuftsmedicalcenter.org

Introduction

The cardiorenal syndrome is a term referring to a complex group of disorders involving dysfunction in both the heart and kidneys. Some definitions have delineated whether the primary dysfunction is stemming from the heart versus the kidney, but in most clinical settings, this distinction is challenging, partly from the interconnection of the pathophysiology between the two organs and partly because many of the pathways remain incompletely understood. For the purpose of this review, we will focus on the cardiorenal syndrome encountered in the hospital setting as defined by declines in kidney function in the setting of acute decompensated heart failure.

Epidemiology and Prognosis

The prevalence of heart failure is estimated around 64.3 million adults worldwide.[1] Kidney dysfunction among patients with heart failure can be considered in two categories: baseline reduced levels of kidney function at the time of admission to the hospital or acute declines in kidney function in the hospital. Baseline CKD, as defined by an eGFR of <60 ml/min per 1.73 m², is prevalent in approximately 60% of patients admitted for acute decompensated heart failure.[2] The presence of CKD is a strong risk factor for adverse outcomes, including mortality and cardiovascular events, with the risk being higher among those with lower baseline eGFR.[3] Acute declines in eGFR, as defined by increases in creatinine ≥0.3 mg/dl or eGFR decline >25%, are observed in approximately 20%–30% of patients admitted for acute decompensated heart failure.[4] In contrast to baseline eGFR, the prognostic significance of acute eGFR declines is more nuanced. Several studies have demonstrated that acute eGFR declines need to be interpreted in the context of decongestion; if there are signs of concomitant decongestion, then an acute eGFR decline is not necessarily associated with worse outcomes. If, however, decongestion is not achieved, an acute eGFR decline is associated with adverse outcomes.[5,6]

Acute decompensated heart failure may progress into cardiogenic shock, as defined in trials as systolic BP <90 mm Hg with evidence of end-organ hypoperfusion.[7] Previous studies of patients with cardiogenic shock have noted an incidence of acute eGFR declines ranging from 33% to 60%, depending on the definition (ranging from an increase in serum creatinine of ≥0.3 mg/dl to doubling of serum creatinine).[8] Acute eGFR declines in cardiogenic shock have been associated with in-hospital mortality rates of approximately 50% across several observational studies.[8]

Pathophysiology

The mechanisms underlying the pathophysiology in the cardiorenal syndrome are not completely

Copyright © 2023 by the American Society of Nephrology

SHOUT
SHARE
IT

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 10/16/2024

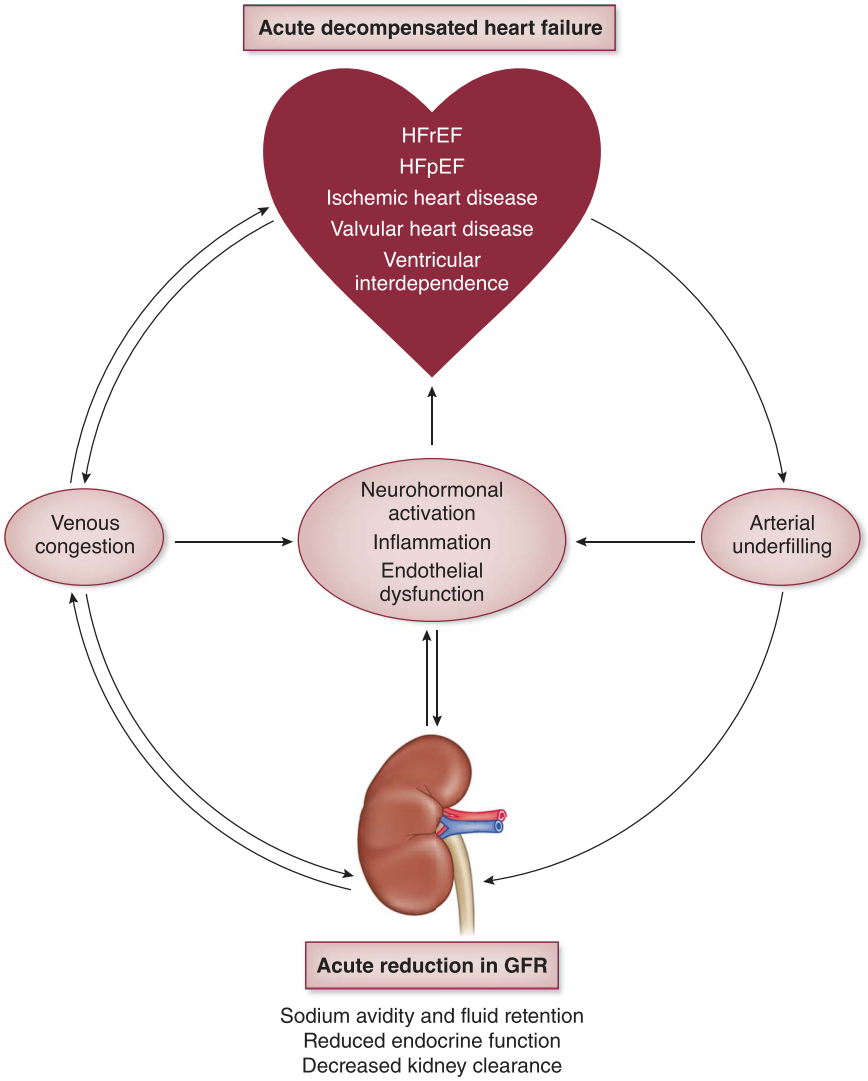

Figure 1. Proposed pathophysiological pathways leading to the cardiorenal syndrome and its complications. The inciting event is usually an acute decompensation of heart failure. This may lead to either arterial underfilling or venous congestion as mediators that promote neurohormonal activity, inflammation, and endothelial dysfunction. In combination, these pathways lead to reductions in glomerular filtration rate. Complications include sodium avidity and fluid retention, reduced kidney clearance, and endocrine function, all of which further perpetuate the pathophysiology. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

understood. There are a number of multidirectional pathways centering on the key aspects of acute decompensation in cardiac function, venous congestion, arterial underfilling, neurohormonal activation, inflammation, and endothelial dysfunction alongside reductions in GFR (Figure 1). The complications of these pathways are intense sodium avidity, fluid retention as well as decreased kidney clearance, and kidney-related endocrine functions. Furthermore, the complications themselves can perpetuate the pathophysiology.

Acute Decompensated Heart Failure as the Inciting Event

While there can be a number of underlying etiologies of cardiomyopathy among patients who develop the cardiorenal syndrome—including ischemic and nonischemic cardiomyopathy, heart failure with reduced ejection fraction, and heart failure with preserved ejection fraction—the cascade of mediating pathways is believed to be initiated by acute decompensation leading to arterial underfilling and/or venous congestion (Figure 1). On the other hand, some theorize that the kidney's inappropriate handling of salt and water may be the inciting event, particularly among patients with heart failure with preserved ejection fraction.[9] Clinical presentations of acute decompensated heart failure can vary from a predominance of left-sided heart failure, right-sided heart failure, or both, particularly given the phenomenon of ventricular interdependence (distended right ventricle impeding diastolic filling of the left ventricle and further diminishing forward flow).

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 10/16/2024

Arterial Underfilling

While the classic teaching had been that eGFR reductions in acute decompensated heart failure stemmed from low cardiac output, there has been increasing literature suggesting it may not be the primary cause in most cases. Studies have shown no clear direct association between cardiac output and either baseline eGFR or acute eGFR declines.[10] Baroreceptors in the aorta do, however, trigger neurohormonal signals in response to low perfusion pressure from arterial underfilling, which will stimulate sodium and water avidity. In this sense, while low cardiac output may not be the major driver of eGFR reductions, it likely contributes to a cascade of maladaptive processes in the cardiorenal syndrome.

Venous Congestion

Several observational studies have shown that venous congestion is associated with reduced eGFR in cross-sectional analyses.[11–13] In some,[11] but not all studies,[14] markers of congestion have also been associated with acute eGFR declines. Animal models have shown intrarenal hemodynamic changes with venous congestion, including reductions in renal blood flow and increase in tubular sodium avidity. Venous congestion may stimulate upregulation of fibrotic pathways in the kidney and also activate endothelial cells to release local neurohormones and cytokines, which will propagate inflammatory pathways.[15–17]

In some patients with acute decompensated heart failure, congestion can manifest as ascites with increased intra-abdominal pressure. Among 40 patients admitted for acute decompensated heart failure, with comparable hemodynamics, those with elevated intra-abdominal pressures of ≥8 mm Hg had higher baseline serum creatinine (2.3±1.0 mg/dl versus 1.5±0.8 mg/dl).[18] This is despite the intra-abdominal pressures being lower than the clinically accepted definition of ≥12 mm Hg for intra-abdominal hypertension. Invasive fluid removal, performed in nine patients, led to decreases in intra-abdominal pressures and improvements in kidney function.

Neurohormonal Activity, Inflammation, and Endothelial Dysfunction

Both arterial underfilling and venous congestion may lead to a number of pathways including neurohormonal activation, inflammation, and endothelial dysfunction (Figure 1). There are multiple neurohormonal pathways that are activated, with examples including the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, and the natriuretic peptide pathway. Arterial underfilling triggers baroreceptors, which activate the RAAS, the sympathetic nervous system, and stimulate arginine vasopressin release, all of which increase sodium and water reabsorption. The macula densa senses a decrease in chloride concentration in the tubular filtrate, triggering renin release from the juxtaglomerular cells as another source of RAAS activation. In addition, levels of adenosine, an endogenous nucleoside, have been shown to increase in states of low perfusion and can induce afferent arteriolar constriction, reductions in GFR, and increases in sodium reabsorption through the A_1 receptors in the kidney.[19] As a counterbalance, congestion can also stimulate the release of natriuretic peptides, which induce natriuresis.[20]

In addition to neurohormones, there are also elevated levels of cytokines and inflammatory biomarkers, including C-reactive protein, tumor necrosis factor-α, and IL-6, all of which are elevated in heart failure and associated with higher risk of mortality.[21,22] Inflammatory cytokines can also be associated with generation of oxidative stress, decreased nitric oxide availability, and likely a host of other mediators leading to endothelial dysfunction, believed to be a key component in the pathophysiology of cardiorenal syndrome.[21]

Complications of Cardiorenal Syndrome

Sodium Avidity, Fluid Retention, and Diuretic Resistance

One of the hallmarks of cardiorenal syndrome is kidney sodium avidity, leading to challenges for decongestion. Although there is no standardized definition for diuretic resistance, the prior literature has used measures of diuresis—weight loss, urine output, or urine sodium—per dose of furosemide loop diuretic.[23,24] The development of diuretic resistance (*i.e.,* requiring escalating doses of loop diuretic to achieve the same degree of urine output) is associated with higher risk of mortality.[25] The pathophysiology is complex and likely due to a combination of reduced GFR, slow plasma refill, chloride depletion triggering renin release, and other triggers for the RAAS and the sympathetic nervous system. In addition, edema in the gut wall can lead to slower absorption of oral diuretics, perpetuating diuretic resistance from a reduction in peak plasma levels.[26] Chronic use of loop diuretics leads to distal tubular hypertrophy, likely further worsening diuretic response.[27,28]

Decreased Kidney Clearance and Endocrine Function

Decreased clearance of uremic toxins, while considered a consequence of the reduced GFR, is believed to mediate some of the pathways in cardiorenal syndrome. Accumulation of uremic toxins including indoxyl sulfate, p-cresyl sulfate, and fibroblast growth factor 23 (FGF-23) have been implicated in endothelial dysfunction, fibrosis, and inflammation.[29–31] Other complications of reduced GFR include reduced erythropoietin production and disordered iron metabolism leading to anemia, which in turn is associated with higher mortality and greater kidney function decline among patients with heart failure.[32,33] Bone and mineral disease abnormalities, including elevations of FGF-23, decreased phosphate excretion, and disordered vitamin D metabolism, primarily result from reduced kidney function and are associated with vascular and endothelial dysfunction.[34]

Diagnostic Testing and Monitoring Strategies in the Cardiorenal Syndrome

Assessment for Alternative Causes of Kidney Function Decline

Certain etiologies of cardiomyopathy such as sarcoidosis, amyloid, or Fabry disease can cause kidney disease distinct from the cardiorenal syndrome but can also lead to the

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 10/16/2024

Table 1. Examples of specific etiologies of cardiomyopathies that may cause kidney disease distinct from the cardiorenal syndrome

Disease	Potential Manifestations			Diagnostic Testing	Treatment
	Kidney	Cardiac	Other		
Fabry disease	Proteinuria, progressive decline in eGFR in early adulthood, family history of kidney failure	Hypertrophic cardiomyopathy	Cornea verticillata, angiokeratoma, strokes	α-GAL activity (male); GLA gene testing (female)	Agalsidase beta replacement therapy (Fabrazyme)
AL amyloidosis	Proteinuria, hematuria, decline in eGFR	Thickened myocardium, low voltage, arrhythmias	Orthostatic hypotension, anemia, lytic bone lesions	Fat pad biopsy, serum light chains, IFE, SPEP	Chemotherapy, stem cell transplant
ATTR amyloidosis	Proteinuria, hematuria, decline in eGFR	Restrictive cardiomyopathy, arrhythmias	Peripheral neuropathy, carpal tunnel	PET scan	Tafamidis
Sarcoidosis	Interstitial nephritis, nephrolithiasis, nephrocalcinosis	Cardiomyopathy, conduction abnormalities, arrhythmias	Granuloma formation, hilar adenopathy	Biopsy	Corticosteroids

Fabry disease is an x-linked lysosomal storage disorder with more severe clinical features in male patients, but women can also present with kidney, cardiac, and neurological manifestations typically at an older age in comparison with men. α-GAL, α-galactosidase; GLA, α-galactosidase A gene; AL, amyloid light-chain; IFE, immunofixation; SPEP, serum protein electrophoresis; PET, positron emission tomography.

hemodynamic and neurohormonal aberrations that would present as the cardiorenal syndrome (Table 1). Careful assessment of the patient's history, longitudinal eGFR trends, presence of albuminuria and proteinuria, review of the urine sediment, and imaging can provide important clues as to whether there is intrinsic kidney disease warranting further evaluation. Spot urine albumin:creatinine ratios need to be interpreted carefully becsause ratios will appear artificially elevated when indexed to urinary creatinine in the midst of AKI since urinary excretion of creatinine will be low; confirmatory studies using 24-hour urine measurements may be required.

Role of Hemodynamic Monitoring

While routine use of invasive hemodynamic monitoring using pulmonary artery catheters was not associated with better survival for patients with acute decompensated heart failure,[35] this study excluded patients with cardiogenic shock. A subsequent observational study of patients with cardiogenic shock from acute decompensated heart failure has shown a mortality benefit with the use of invasive hemodynamic monitoring.[36] Declines in kidney function in the midst of treatment for acute decompensated heart failure is now cited as one of several clinical parameters that should prompt placement of a pulmonary artery catheter.[37]

Point-of-Care Ultrasound and Other Noninvasive Methods of Volume Assessment

There are many challenges in assessing volume status for patients with acute decompensated heart failure, with poor correlation between physical examination findings and invasive measures of congestion.[38,39] Point-of-care ultrasound has been increasingly adapted in certain settings, including the emergency department and intensive care unit, for noninvasive assessment of volume status. Evaluation of venous blood flow patterns by Doppler ultrasound (inferior vena cava, hepatic and portal veins, and intrarenal veins) has been investigated as a technique to identify venous congestion.[40] Particularly, patterns of intrarenal venous blood flow have been shown to correlate with congestion among patients with acute decompensated heart failure and have been associated with worse survival, suggesting that this modality should be studied further as a prognostic and potentially a management tool.[41,42] Bioelectrical impedance vector analysis has been suggested as another noninvasive method to quantify total body water on the basis of electrical resistance vector patterns[43]; however, its widespread utility has been limited given the high prevalence of implantable cardiac devices among patients with heart failure. Intra-abdominal pressure can be measured using an indwelling urinary Foley catheter connected to a pressure transducer.

Biomarkers

It is well recognized that a rise in serum creatinine can be a relatively delayed finding in cases of kidney injury; furthermore, it may not represent intrinsic kidney injury, but rather a hemodynamic change in GFR. Some studies have evaluated kidney tubular injury biomarkers—including kidney injury molecule-1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), and neutrophil gelatinase-associated lipocalin (NGAL)—and have shown no rise in these injury biomarkers despite rises in creatinine with decongestion, suggestive that these creatinine increases were hemodynamic.[44] Other studies have observed elevated levels of KIM-1, NAG, and NGAL with decongestion, but the elevated levels were not associated with mortality or longer-term declines in kidney function.[45] Given the inconsistency of the results, the use of kidney

injury biomarkers is not currently recommended for routine clinical practice.

Therapies for the Cardiorenal Syndrome

Decongestion

Targeting Tubular Sodium Avidity

Previous studies have shown that achievement of decongestion during hospitalization is associated with improved clinical outcomes, making it an important priority.[46] The ideal target rate of decongestion remains a question, but at least in observational studies, proxies of more rapid decongestion were not associated with longer-term kidney harm or mortality risk[47,48] nor has there been evidence of consistent increase in RAAS levels with decongestion.[49]

Intense tubular sodium avidity requires judicious use of diuretics and combining of agents with varying pharmacological targets. The first step is usually intravenous loop diuretics, which block the Na-K-2Cl channel. The Diuretic Optimization Strategies Evaluation (DOSE) trial demonstrated that there was no difference in the improvement of symptoms with bolus versus continuous dosing but that there was a trend toward improvement with high dose (2.5×home daily dose) than low dose (same as home daily dose) but with associated increases in serum creatinine (Table 2).[50] For guidance for dose escalation, a few studies have shown that a spot urinary sodium excretion of <50–60 mmol/L a few hours after diuretic administration was associated with poor diuretic response and thereby may provide a clue for earlier identification of patients in need of either higher loop diuretic dosing or addition of a thiazide diuretic.[51,52] Thiazide diuretics, which target the Na-Cl cotransporter in the distal convoluted tubule, are important agents to use in combination with loop diuretics to sequentially block sodium reabsorption. The efficacy of using hydrochlorothiazide with a loop diuretic was examined in the Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC) trial, which randomized 230 patients admitted for acute decompensated heart failure to either thiazide plus loop or loop diuretic alone.[53] It showed greater weight loss in the combined arm, but with higher rates of a rise in serum creatinine >0.3 mg/dl. A number of observational studies have shown thiazide diuretics to be efficacious in acute decompensated heart failure, even at low GFR.[54]

Other strategies to augment natriuresis have been studied. Sodium-glucose cotransporter 2 inhibitors (SGLT2i), which enhance natriuresis by blocking proximal tubular sodium reabsorption, are one such option. Despite the wide uptake and efficacy of SGLT2i therapy for chronic outpatients with heart failure with both reduced and preserved ejection fraction,[55,56] the safety and benefits of SGLT2i in the acute setting are less clear. The EMPULSE study randomized 530 patients with acute decompensated heart failure to empagliflozin 10 mg versus placebo in addition to other heart failure therapy.[57] Empagliflozin decreased the risk of death and heart failure hospitalization (primary outcome) and also resulted in greater weight loss.

Acetazolamide, an inhibitor of carbonic anhydrase, has also been evaluated to augment diuresis. Studies at the cellular level have shown that blockade of carbonic anhydrase with acetazolamide will also inhibit activity of the sodium/hydrogen exchanger, leading to enhanced natriuresis.[58] The Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial randomized 519 patients admitted for acute decompensated heart failure to treatment with acetazolamide versus placebo in addition to loop diuretic therapy.[59] More patients in the acetazolamide arm met the primary outcome, defined as successful decongestion (absence of signs of volume overload) by 3 days as compared with the placebo arm (42.2% versus 30.5%). Despite the improved decongestion, there was no difference in all-cause mortality or heart failure hospitalization at 3 months. As far as generalizability, it is important to note that protocols in this trial did not include the use of thiazides or SGLT2 inhibitors.

Targeting the Neurohormonal System

Agents that target the neurohormonal system have also been studied. The Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial randomized 360 patients with acute decompensated heart failure to treatment with high-dose spironolactone (100 mg) versus placebo or low-dose spironolactone (25 mg).[60] While the intervention was safe from the perspective of hyperkalemia or acute eGFR declines, there was no difference in diuresis or weight loss in the hospital or mortality or heart failure hospitalization at 60 days. Tolvaptan, a direct vasopressin V2 antagonist, has been associated with greater degree of urine output and weight loss when added to standard therapy.[61,62] There was no evidence of benefit for mortality or heart failure hospitalization overall.[63] For targeting the natriuretic peptide system, infusions of human recombinant brain natriuretic peptide in the form of nesiritide have been examined, with the hypothesis that vasodilation and natriuretic properties would help facilitate renal blood flow and natriuresis. While small studies did show improvements in cardiac hemodynamics, larger studies showed no difference in urine output, kidney function, or mortality.[64,65] Rolofylline, an adenosine A_1 receptor antagonist, is hypothesized to increase renal blood flow and prevent GFR decline as well as enhance natriuresis. However, it did not show any differences in survival or changes in eGFR in a large randomized control trial.[66]

Hypertonic saline administration has also been evaluated in acute decompensated heart failure. While the studies to date have been relatively small or from the same center, they have shown that a small bolus of 1.4%–4.6% saline (150 ml) administered with loop diuretics resulted in an increase in urine output and weight loss.[67,68] The proposed mechanism is several-fold: (*1*) osmotic forces helping to mobilize fluid from the interstitial space to the intravascular space because of the osmolar load of the hypertonic saline; (*2*) improvement in renal blood flow; and (*3*) reduction in the degree of RAAS stimulation. The macula densa may in fact be responding to the chloride content of the sodium chloride bolus, halting tubular glomerular feedback and renin release.

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 10/16/2024

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 10/16/2024

Table 2. Examples of trials of decongestion strategies for acute decompensated heart failure

Class of Drug or Diuretic Strategy	Trial	Year	No. of Patients	Intervention	Kidney-Related Exclusion Criteria	Summary of Key Findings
Loop diuretic dosing strategy[50]	DOSE	2011	308	Bolus versus continuous loop diuretic strategy; low (same as home) versus high dose (2.5× home dose)	Creatinine >3 mg/dl	No significant difference in dyspnea with bolus versus continuous dosing. Trend toward improvement with high dose over low dose. Higher rates of creatinine >0.3 mg/dl in the high dose (23%) versus low dose (14%) at 72 h
Thiazide plus loop[53]	CLOROTIC	2022	230	Hydrochlorothiazide (25, 50, or 100 mg) plus loop diuretic versus placebo plus loop diuretic	Kidney failure requiring dialysis Sodium ≤125 mmol/L	Weight loss was greater in the thiazide versus placebo arm (−2.3 versus −1.5 kg) at 72 h. Higher rates of rise in creatinine by >0.3 mg/dl in thiazide arm (46.5%) versus placebo (17.2%)
SGLT2 inhibitor[57]	EMPULSE	2022	530	Empaglifozin 10 mg once daily versus placebo for patients no longer requiring escalation of IV diuretic dosing or use of IV vasodilators or inotropes	eGFR <20 ml/min per 1.73 m^2	Empagliflozin showed a greater win ratio of 1.36 over placebo for components of the primary outcome of time to death and frequency of heart failure exacerbations. Greater diuretic response (−2.31 [−3.77 to −0.85] kg more in weight loss per mean daily loop diuretic dose) in the empagliflozin versus placebo arm
Mineralocorticoid receptor antagonist[60]	ATHENA	2017	360	Spironolactone 100 mg or 25 mg versus placebo (plus standard therapy) for 4 d	eGFR <30 ml/min per 1.73 m^2 K >5.0 mmol/L	No significant difference in the primary outcome of change in NT-proBNP levels. No difference in cumulative net urine output or weight change
Nesiritide[64]	ASCEND-HF	2011	7141	Nesiritide bolus of 2 μg/kg followed by 0.01 μg/kg per min versus placebo (plus standard therapy) for 1–7 d	Kidney failure requiring dialysis	No significant difference in rates of all-cause mortality (3.6% versus 4%) or rates of eGFR decline by >25% (31.4% versus 29.5%) in nesiritide or placebo arms, respectively
Nesiritide or dopamine[65]	ROSE	2013	360	Nesiritide 0.005 μg/kg per min versus dopamine 2 μg/kg per min versus placebo (plus standard therapy) for 3 d	eGFR <15 or >60 ml/min per 1.73 m^2	No significant difference in cumulative urine output or changes in cystatin C at 72 h

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 10/16/2024

Table 2. (Continued)

Class of Drug or Diuretic Strategy	Trial	Year	No. of Patients	Intervention	Kidney-Related Exclusion Criteria	Summary of Key Findings
Carbonic anhydrase inhibitor[59]	ADVOR	2022	519	Acetazolamide 500 mg IV daily versus placebo (plus standard therapy) for 3 d for patients not receiving thiazides or SGLT2i therapy	eGFR <20 ml/min per 1.73 m^2	Greater rates of decongestion (no edema, pleural effusion, or ascites) in the acetazolamide arm (42.2%) versus the placebo arm (30.5%) at 3 d. No significant difference in secondary outcome of mortality or heart failure rehospitalization. No significant difference in rates of a combined kidney safety end point[a]
Vasopressin V2 antagonist[63]	ACTIV in CHF	2007	319	Tolvaptan 30 mg, 60 mg, 90 mg daily versus placebo (plus standard therapy)	Creatinine >3.5 mg/dl	Greater weight loss in tolvaptan arm that was sustained after hospitalization. No significant difference in the secondary outcome of heart failure hospitalization. No differences in serum creatinine at the time of discharge
Hypertonic saline[68]	HHS	2005	94	150 ml IV of hypertonic saline (1.4%–4.6% NaCl) twice daily plus furosemide versus furosemide alone for patients unresponsive to furosemide 250–500 mg/d	Creatinine >2 mg/dl	Faster reduction in BNP levels and greater amount of urine output in the hypertonic saline plus furosemide arm (2.2±0.5) versus furosemide alone arm (1.5±0.4) L/d
Hypertonic saline[67]	SMAC-HF	2011	1771	150 ml IV of hypertonic saline (1.4%–4.6% NaCl) twice daily versus no hypertonic saline (plus standard therapy with furosemide)	Creatinine >2.5 mg/dl	Lower rates of cardiovascular mortality in the hypertonic saline arm (12.9%) versus the diuretic-only arm (23.8%)
UF[69]	UNLOAD	2007	100	UF (variable rate, average of 241 ml/h) versus pharmacological therapy	Creatinine >3 mg/dl	Net fluid loss was greater in the UF arm (4.6±2.6 L) versus pharmacological arm (3.3±2.6 L) at 48 h. No difference in rates of creatinine rise by ≥0.3 mg/dl (26.5% versus 20.5%) in the UF versus pharmacological arms, respectively
UF[70]	CARRESS	2012	188	UF (fixed at 200 ml/h) versus stepped diuretic protocol for those demonstrating creatinine rise of ≥0.3 mg/dl	Creatinine >3.5 mg/dl	No significant difference in weight loss at 96 h. Significantly different change in creatinine at 96 h, with mean increase of 0.23±0.7 mg/dl in the UF arm versus −0.04±0.5 mg/dl in the pharmacological arm

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 10/16/2024

Table 2. (Continued)

Class of Drug or Diuretic Strategy	Trial	Year	No. of Patients	Intervention	Kidney-Related Exclusion Criteria	Summary of Key Findings
UF[71]	AVOID-HF	2016	224	UF (variable rate, average of 138 ml/h) versus stepped diuretic protocol	Creatinine >3 mg/dl	No significant difference in the primary outcome of time to a heart failure rehospitalization or unscheduled visit for heart failure. No difference in changes in creatinine at 90 d or rates of kidney failure requiring dialysis (0.9% versus 0.9% in each arm)

DOSE, Diuretic Optimization Strategies Evaluation; CLOROTIC, Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure; SGLT2, sodium-glucose cotransporter 2; EMPULSE, EMPagliflozin 10 mg compared with placebo, initiated in patients hospitalized for acUte heart faiLure who have been StabilizEd; ATHENA, Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure; ASCEND-HF, Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; NT-proBNP, N-terminal pro–B-type natriuretic peptide; ROSE, Renal Optimization Strategies Evaluation; ADVOR, Acetazolamide in Decompensated Heart Failure with Volume Overload; ACTIV in CHF, Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure; HHS, hypertonic saline solution; SMAC-HF, Self-Management and Care of Heart Failure; SGLT2i, SGLT2 inhibitor; NaCl, sodium chloride; UF, ultrafiltration; UNLOAD, Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure; CARRESS, Cardiorenal Rescue Study in Acute Decompensated Heart Failure; AVOID-HF, Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure.

[a]Combined safety end point of doubling of serum creatinine, ≥50% sustained decrease in eGFR, or need for KRT during hospitalization.

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 10/16/2024

Invasive Methods

There are also several scenarios in which escalation to invasive means of fluid removal, either ultrafiltration (UF) or KRT, is indicated. These include volume overload despite up-titration of diuretic therapy, requirement for rapid fluid removal that cannot be achieved with medical therapy alone, or electrolyte and/or other uremic indications for KRT. The Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial randomized 200 patients with acute decompensated heart failure to management with UF versus standard diuretic therapy, with a flexible UF rate.[69] The results showed fewer heart failure hospitalizations in the UF arm. However, the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS) trial, which selected patients with the cardiorenal syndrome by evidence of an >0.3 mg/dl increase in serum creatinine before randomization, noted no difference in mortality and higher rates of complications in the UF arm (UF rate was fixed at 200 ml/h).[70] In the Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure (AVOID-HF) trial, in which investigators could adjust the UF rate up to a maximum rate of 500 ml/h (similar to UNLOAD), UF also did not show any mortality benefit over diuretic therapy and was associated with slightly higher rates of complications.[71] With the inconsistency between these three major trials, clinical guidance has centered around the use of pharmacological therapy until there are no further options to overcome diuretic resistance outside of invasive UF. The ongoing trial REVERSE-HF (NCT05318105), which is anticipated to randomize 372 participants with acute decompensated heart failure to either UF or IV diuresis, may help provide more data.

Peritoneal dialysis (PD) is an alternative option for fluid removal in cases of diuretic resistance. For patients with CKD stage 4, there have been a number of observational studies demonstrating that PD can alleviate heart failure symptoms and reduce heart failure hospitalizations.[72,73] As opposed to hemodialysis, where large and rapid volume shifts can lead to hemodynamic instability and possibly worsening of residual kidney function, PD may be better tolerated.

Increasing Cardiac Output

While decreased cardiac output may not be the sole culprit of the cardiorenal syndrome, it certainly triggers a cascade of compensatory responses. Furthermore, in cardiogenic shock, increasing the cardiac output to restore end-organ perfusion is an urgent goal. Strategies for increasing cardiac output include the use of inotropes including milrinone or dobutamine. If patients in cardiogenic shock do not show improvement with medical therapy, management strategies may include mechanical circulatory support including intra-aortic balloon pump, left ventricular support devices including Impella or left ventricular assist device (LVAD), right heart–specific devices such as right ventricular assist device or Impella RV, or complete support with biventricular assist device or venoarterial extracorporeal membrane oxygenation. Patient selection depends on many factors, including prognosis for recovery and future eligibility for heart transplant. Each device poses particular considerations regarding kidney function (Table 3), including device positioning in the case of intra-aortic balloon pump (balloon inflation at the level of renal arteries could block renal arterial blood flow) and hemolysis-related pigment-induced AKI in the case of an Impella. Regarding biventricular assist device or venoarterial extracorporeal membrane oxygenation, patients requiring such high levels of circulatory support are extremely ill and at higher risk for multiorgan failure including progressive kidney injury.

Mechanical circulatory support devices that are longer-term, namely LVADs (*e.g.*, HeartMate3 and HeartMateII), are referred to as "durable" support for patients with advanced heart failure. Between 2010 and 2019, over 27,000 LVADs have been placed.[74] The 2022 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) guidelines no longer list CKD or kidney failure as contraindications for LVAD. However, for patients with kidney failure requiring long-term dialysis (*i.e.*, not AKI requiring short-term dialysis), two observational studies have shown in-hospital mortality rates as high as 40%–50% after LVAD placement—something to be considered in the discussions surrounding suitability of LVAD implantation.[75,76] For patients not requiring dialysis, studies examining the changes in eGFR after LVAD have shown that approximately three-quarters of patients will have an improvement in eGFR in the initial month post-LVAD, but nearly all show slow but progressive eGFR decline in the year after LVAD, including among those with initial increases.[77] There are several hypotheses to the progressive eGFR decline despite the hemodynamic LVAD support. These include but are not limited to (*1*) eGFR decline in the setting of chronic ischemia and perhaps tubular injury; (2) chronic hemolysis leading to hemoglobinuria and pigment nephropathy on the basis of a case report of hemosiderin deposition in a kidney biopsy[78]; and (3) chronic vascular injury from the continuous blood flow pattern that is generated by some LVADs (*i.e.*, HeartMateII). In fact, animal models have shown proliferation of smooth muscle cells and medial fibrosis with continuous flow.[79] However, the eGFR decline has also been observed with pulsatile flow, which is a feature of other LVAD models including the HeartMate3.[77] The development of AKI requiring dialysis after LVAD placement is associated with poor prognosis, with studies reporting 40%–75% 1-year mortality (compared with the average 1-year mortality of 7% for all LVAD recipients).[80] For patients who survive, maintenance dialysis after LVAD implantation requires support and training of dialysis staff for monitoring of LVAD flow parameters during dialysis and management of alarms and emergencies. PD may be better tolerated from a hemodynamic perspective, including avoidance of low flow alarms, but it is important that all components of the LVAD, including the drivelines and pump pockets, do not violate the peritoneum—which they typically do not.[73] Furthermore, as with HD, there is a need of wider availability and training of staff throughout all levels of health care for patients with LVADs receiving PD.

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 10/16/2024

Table 3. Mechanical circulatory support devices and kidney considerations

Type of Circulatory Support	MCS Device	Pump Mechanism	Device Placement[a]		Hemodynamic Effects		Device-Specific Kidney Considerations
			Inflow	Outflow	Stroke Volume	Afterload	
LV support	IABP	Pneumatic	Ascending aorta	Descending aorta	Slight increase	Decrease	Malposition can block renal arteries if too distal, and risk of emboli of atherosclerotic debris
	Impella 2.5, CP, 5.5	Axial	Left ventricle	Aortic root	Increase	Neutral	Risk of hemolysis at higher performance levels or with malposition
	TandemHeart	Centrifugal	Left atrium	Femoral artery	Increase	Increase	—
RV support	Impella RP	Axial	Right atrium	Pulmonary artery	Increase	Neutral	Risk of hemolysis at higher performance levels or with malposition
	TandemHeart RVAD	Centrifugal	Right atrium	Pulmonary artery	Increase	Increase	—
BiV support	VA ECMO	Centrifugal	Right atrium	Femoral artery	Increase	Increase	Risk of hemolysis, rhabdomyolysis from limb ischemia
	CentriMag	Centrifugal	Right atrium/left atrium	Pulmonary artery/ aorta	Increase	Neutral	—
Durable LVAD	HeartMate3	Centrifugal with levitating magnet	Left ventricle	Ascending aorta	Increase	Neutral	Pulsatile flow, which may be more physiological for the kidney and other organs
	HeartMateII	Axial	Left ventricle	Ascending aorta	Increase	Neutral	Continuous flow, hypothesized link to medial hyperplasia

Pneumatic pump mechanism referring to deflation during systole causing a vacuum effect and indirectly increases forward flow from the heart. Axial flow pumps will direct blood flow along a path parallel to the axis of the device. Centrifugal flow pumps will direct blood flow through a circuit generated by a rotating configuration of blades. Durable referring to circulatory support devices that can remain in place long term (*i.e.*, outside of the hospital). MCS, mechanical circulatory support; LV, left ventricular; IABP, intra-aortic balloon pump; RV, right ventricular; RVAD, right ventricular assist device; BiV, biventricular; VA ECMO, venoarterial extracorporeal membrane oxygenation; LVAD, left ventricular assist device.
[a]These are the anatomic locations where devices are generally placed, but cannulation can be variable.

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 10/16/2024

Future Considerations

There are numerous studies investigating a range of novel agents for treatment of the cardiorenal syndrome. These include pharmacological agents to induce vasodilation, monoclonal antibodies that target inflammatory cytokines, and augmentation of the innate and humoral immune system to combat inflammation and endothelial dysfunction. Another area of investigation is diuretic resistance, with trials of pharmacological agents to increase diuretic response (*e.g.*, lysine chloride), and nondiuretic methods to remove salt and water such as through peritoneal zero sodium dialysate. For device-based therapies, there are devices under investigation to decrease cardiac preload and afterload, increase kidney preload by increasing renal artery perfusion, and decrease kidney afterload by either propelling blood from the renal vein or decompressing renal intracapsular pressure.[81]

The cardiorenal syndrome is a complex collection of bidirectional pathways involving declining heart and kidney function. While the exact pathophysiological mechanisms need better understanding, they center around venous congestion, arterial underfilling, neurohormonal activity, inflammation, and endothelial dysfunction. Strategies to mitigate the sodium and fluid avidity include up-titration of diuretic therapy and escalation to invasive means. In more advanced cases of cardiogenic shock, there are increasing opportunities to use mechanical circulatory support devices.

Disclosures

M.J. Sarnak reports consultancy agreements with Cardurian; sits on the steering committee of Akebia, with funds paid to Tufts Medical Center; and reports research funding from NIH. M.J. Sarnak's spouse is an employee of Lilly. The remaining author has nothing to disclose.

Funding

National Center for Advancing Translational Sciences TR002545-04.

Author Contributions

W. McCallum and M.J. Sarnak wrote the original draft and reviewed and edited the manuscript.

References

1. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392(10159):1789–1858. doi:10.1016/S0140-6736(18)32279-7
2. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J. High prevalence of renal dysfunction and its impact on outcome in 118, 465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. *J Card Fail.* 2007;13(6):422–430. doi:10.1016/j.cardfail.2007.03.011
3. Fonarow GC, Adams KF, Abraham WT, Yancy CW, Boscardin WJ; ADHERE Scientific Advisory Committee, Study Group, and Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA.* 2005;293(5):572–580. doi:10.1001/jama.293.5.572
4. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol.* 2004;43(1):61–67. doi:10.1016/j.jacc.2003.07.031
5. McCallum W, Tighiouart H, Testani JM, et al. Acute kidney function declines in the context of decongestion in acute decompensated heart failure. *JACC Heart Fail.* 2020;8(7):537–547. doi:10.1016/j.jchf.2020.03.009
6. Metra M, Cotter G, Senger S, et al. Prognostic significance of creatinine increases during an acute heart failure admission in patients with and without residual congestion: a post hoc analysis of the PROTECT data. *Circ Heart Fail.* 2018;11(5):e004644. doi:10.1161/CIRCHEARTFAILURE.117.004644
7. van Diepen S, Katz JN, Albert NM, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation.* 2017;136(16):e232–e268. doi:10.1161/CIR.0000000000000525
8. Sheikh O, Nguyen T, Bansal S, Prasad A. Acute kidney injury in cardiogenic shock: a comprehensive review. *Catheter Cardiovasc Interv.* 2021;98(1):E91–E105. doi:10.1002/ccd.29141
9. Hung SC, Lai YS, Kuo KL, Tarng DC. Volume overload and adverse outcomes in chronic kidney disease: clinical observational and animal studies. *J Am Heart Assoc.* 2015;4(5):e001918. doi:10.1161/JAHA.115.001918
10. Hanberg JS, Sury K, Wilson FP, et al. Reduced cardiac index is not the dominant driver of renal dysfunction in heart failure. *J Am Coll Cardiol.* 2016;67(19):2199–2208. doi:10.1016/j.jacc.2016.02.058
11. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol.* 2009;53(7):589–596. doi:10.1016/j.jacc.2008.05.068
12. Testani JM, Khera AV, St John Sutton MG, et al. Effect of right ventricular function and venous congestion on cardiorenal interactions during the treatment of decompensated heart failure. *Am J Cardiol.* 2010;105(4):511–516. doi:10.1016/j.amjcard.2009.10.020
13. Aronson D, Abassi Z, Allon E, Burger AJ. Fluid loss, venous congestion, and worsening renal function in acute decompensated heart failure. *Eur J Heart Fail.* 2013;15(6):637–643. doi:10.1093/eurjhf/hft036
14. Nohria A, Hasselblad V, Stebbins A, et al. Cardiorenal interactions: insights from the ESCAPE trial. *J Am Coll Cardiol.* 2008;51(13):1268–1274. doi:10.1016/j.jacc.2007.08.072
15. Ganda A, Onat D, Demmer RT, et al. Venous congestion and endothelial cell activation in acute decompensated heart failure. *Curr Heart Fail Rep.* 2010;7(2):66–74. doi:10.1007/s11897-010-0009-5
16. Shimada S, Hirose T, Takahashi C, et al. Pathophysiological and molecular mechanisms involved in renal congestion in a novel rat model. *Sci Rep.* 2018;8(1):16808. doi:10.1038/s41598-018-35162-4
17. Kitani T, Kidokoro K, Nakata T, et al. Kidney vascular congestion exacerbates acute kidney injury in mice. *Kidney Int.* 2022;101(3):551–562. doi:10.1016/j.kint.2021.11.015
18. Mullens W, Abrahams Z, Skouri HN, et al. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? *J Am Coll Cardiol.* 2008;51(3):300–306. doi:10.1016/j.jacc.2007.09.043
19. Vallon V, Mühlbauer B, Osswald H. Adenosine and kidney function. *Physiol Rev.* 2006;86(3):901–940. doi:10.1152/physrev.00031.2005
20. Lee CYW, Burnett JC. Natriuretic peptides and therapeutic applications. *Heart Fail Rev.* 2007;12(2):131–142. doi:10.1007/s10741-007-9016-3
21. Chen D, Assad-Kottner C, Orrego C, Torre-Amione G. Cytokines and acute heart failure. *Crit Care Med.* 2008;36(suppl l):S9–S16. doi:10.1097/01.CCM.0000297160.48694.90
22. Zhang J, Bottiglieri T, McCullough PA. The central role of endothelial dysfunction in cardiorenal syndrome. *Cardiorenal Med.* 2017;7(2):104–117. doi:10.1159/000452283
23. Kiernan MS, Stevens SR, Tang WW, et al. Determinants of diuretic responsiveness and associated outcomes during acute heart failure hospitalization: an analysis from the NHLBI Heart Failure Network Clinical Trials. *J Card Fail.* 2018;24(7):428–438. doi:10.1016/j.cardfail.2018.02.002

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 10/16/2024

24. Testani JM, Brisco MA, Turner JM, et al. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. *Circ Heart Fail.* 2014;7(2):261–270. doi:10.1161/CIRCHEARTFAILURE.113.000895
25. H Verbrugge F, Dupont M, B Bertrand P, et al. Determinants and impact of the natriuretic response to diuretic therapy in heart failure with reduced ejection fraction and volume overload. *Acta Cardiol.* 2015;70(3):265–273. doi:10.1080/ac.70.3.3080630
26. Vargo DL, Kramer WG, Black PK, Smith WB, Serpas T, Brater DC. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. *Clin Pharmacol Ther.* 1995;57(6):601–609. doi:10.1016/0009-9236(95)90222-8
27. Brater DC. Diuretic pharmacokinetics and pharmacodynamics. In: *Diuretic Agents: Clinical Physiology and Pharmacology*. Seldin DW, Giebisch G, eds. Academic Press; 1997:189–208.
28. Abdallah JG, Schrier RW, Edelstein C, Jennings SD, Wyse B, Ellison DH. Loop diuretic infusion increases thiazide-sensitive Na(+)/Cl(-)-cotransporter abundance: role of aldosterone. *J Am Soc Nephrol.* 2001;12(7):1335–1341. doi:10.1681/ASN.V1271335
29. Lekawanvijit S, Kompa AR, Wang BH, Kelly DJ, Krum H. Cardiorenal syndrome: the emerging role of protein-bound uremic toxins. *Circ Res.* 2012;111(11):1470–1483. doi:10.1161/CIRCRESAHA.112.278457
30. Ivey-Miranda JB, Stewart B, Cox ZL, et al. FGF-23 (fibroblast growth factor-23) and cardiorenal interactions. *Circ Heart Fail.* 2021;14(11):e008385. doi:10.1161/CIRCHEARTFAILURE.121.008385
31. Juni RP, Al-Shama R, Kuster DWD, et al. Empagliflozin restores chronic kidney disease-induced impairment of endothelial regulation of cardiomyocyte relaxation and contraction. *Kidney Int.* 2021;99(5):1088–1101. doi:10.1016/j.kint.2020.12.013
32. Young JB, Abraham WT, Albert NM, et al. Relation of low hemoglobin and anemia to morbidity and mortality in patients hospitalized with heart failure (insight from the OPTIMIZE-HF registry). *Am J Cardiol.* 2008;101(2):223–230. doi:10.1016/j.amjcard.2007.07.067
33. Bansal N, Tighiouart H, Weiner D, et al. Anemia as a risk factor for kidney function decline in individuals with heart failure. *Am J Cardiol.* 2007;99(8):1137–1142. doi:10.1016/j.amjcard.2006.11.055
34. Ronco C, Cozzolino M. Mineral metabolism abnormalities and vitamin D receptor activation in cardiorenal syndromes. *Heart Fail Rev.* 2012;17(2):211–220. doi:10.1007/s10741-011-9232-8
35. Binanay C, Califf RM, Hasselblad V, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA.* 2005;294(13):1625–1633. doi:10.1001/jama.294.13.1625
36. Garan AR, Kanwar M, Thayer KL, et al. Complete hemodynamic profiling with pulmonary artery catheters in cardiogenic shock is associated with lower in-hospital mortality. *JACC Heart Fail.* 2020;8(11):903–913. doi:10.1016/j.jchf.2020.08.012
37. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *Circulation.* 2022;145(18):e895–e1032. doi:10.1161/CIR.0000000000001063
38. Testani JM, Brisco MA, Kociol RD, et al. Substantial discrepancy between fluid and weight loss during acute decompensated heart failure treatment. *Am J Med.* 2015;128(7):776–783.e4. doi:10.1016/j.amjmed.2014.12.020
39. Thibodeau JT, Drazner MH. The role of the clinical examination in patients with heart failure. *JACC Heart Fail.* 2018;6(7):543–551. doi:10.1016/j.jchf.2018.04.005
40. Beaubien-Souligny W, Benkreira A, Robillard P, et al. Alterations in portal vein flow and intrarenal venous flow are associated with acute kidney injury after cardiac surgery: a prospective observational cohort study. *J Am Heart Assoc.* 2018;7(19):e009961. doi:10.1161/JAHA.118.009961
41. Iida N, Seo Y, Sai S, et al. Clinical implications of intrarenal hemodynamic evaluation by Doppler ultrasonography in heart failure. *JACC Heart Fail.* 2016;4(8):674–682. doi:10.1016/j.jchf.2016.03.016
42. Ter Maaten JM, Dauw J, Martens P, et al. The effect of decongestion on intrarenal venous flow patterns in patients with acute heart failure. *J Card Fail.* 2021;27(1):29–34. doi:10.1016/j.cardfail.2020.09.003
43. Santarelli S, Russo V, Lalle I, et al. Prognostic value of decreased peripheral congestion detected by Bioelectrical Impedance Vector Analysis (BIVA) in patients hospitalized for acute heart failure: BIVA prognostic value in acute heart failure. *Eur Heart J Acute Cardiovasc Care.* 2017;6(4):339–347. doi:10.1177/2048872616641281
44. Ahmad T, Jackson K, Rao VS, et al. Worsening renal function in patients with acute heart failure undergoing aggressive diuresis is not associated with tubular injury. *Circulation.* 2018;137(19):2016–2028. doi:10.1161/CIRCULATIONAHA.117.030112
45. Rao VS, Ahmad T, Brisco-Bacik MA, et al. Renal effects of intensive volume removal in heart failure patients with preexisting worsening renal function. *Circ Heart Fail.* 2019;12(6):e005552. doi:10.1161/CIRCHEARTFAILURE.118.005552
46. Lala A, McNulty SE, Mentz RJ, et al. Relief and recurrence of congestion during and after hospitalization for acute heart failure: insights from Diuretic Optimization Strategy Evaluation in Acute Decompensated Heart Failure (DOSE-AHF) and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF). *Circ Heart Fail.* 2015;8(4):741–748. doi:10.1161/CIRCHEARTFAILURE.114.001957
47. McCallum W, Tighiouart H, Testani JM, et al. Rates of reversal of volume overload in hospitalized acute heart failure: association with long-term kidney function. *Am J Kidney Dis.* 2022;80(1):65–78. doi:10.1053/j.ajkd.2021.09.026
48. McCallum W, Tighiouart H, Testani JM, et al. Rates of in-hospital decongestion and association with mortality and cardiovascular outcomes among patients admitted for acute heart failure. *Am J Med.* 2022;135:e337–e352. doi:10.1016/j.amjmed.2022.04.003
49. Mentz RJ, Stevens SR, DeVore AD, et al. Decongestion strategies and renin-angiotensin-aldosterone system activation in acute heart failure. *JACC Heart Fail.* 2015;3(2):97–107. doi:10.1016/j.jchf.2014.09.003
50. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med.* 2011;364(9):797–805. doi:10.1056/NEJMoa1005419
51. Luk A, Groarke JD, Desai AS, et al. First spot urine sodium after initial diuretic identifies patients at high risk for adverse outcome after heart failure hospitalization. *Am Heart J.* 2018;203:95–100. doi:10.1016/j.ahj.2018.01.013
52. Testani JM, Hanberg JS, Cheng S, et al. Rapid and highly accurate prediction of poor loop diuretic natriuretic response in patients with heart failure. *Circ Heart Fail.* 2016;9(1):e002370. doi:10.1161/CIRCHEARTFAILURE.115.002370
53. Trullàs JC, Morales-Rull JL, Casado J, et al. Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. *Eur Heart J.* 2022;24:ehac689. doi:10.1093/eurheartj/ehac689
54. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. *J Am Coll Cardiol.* 2010;56(19):1527–1534. doi:10.1016/j.jacc.2010.06.034
55. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med.* 2020;383(15):1413–1424. doi:10.1056/NEJMoa2022190
56. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* 2021;385:1451–1461. doi:10.1056/NEJMoa2107038
57. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med.* 2022;28(3):568–574. doi:10.1038/s41591-021-01659-1
58. Krishnan D, Liu L, Wiebe SA, Casey JR, Cordat E, Alexander RT. Carbonic anhydrase II binds to and increases the activity of the epithelial sodium-proton exchanger, NHE3. *Am J Physiol Ren Physiol.* 2015;309(4):F383–F392. doi:10.1152/ajprenal.00464.2014

59. Mullens W, Dauw J, Martens P, et al. Acetazolamide in acute decompensated heart failure with volume overload. *N Engl J Med.* 2022;387(13):1185–1195. doi:10.1056/NEJMoa2203094
60. Butler J, Anstrom KJ, Felker GM, et al. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. *JAMA Cardiol.* 2017;2(9):950–958. doi:10.1001/jamacardio.2017.2198
61. Konstam MA, Gheorghiade M, Burnett JC, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA.* 2007;297(12):1319–1331. doi:10.1001/jama.297.12.1319
62. Gheorghiade M, Konstam MA, Burnett JC, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA.* 2007;297(12):1332–1343. doi:10.1001/jama.297.12.1332
63. Gheorghiade M, Niazi I, Ouyang J, et al. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. *Circulation.* 2003;107(21):2690–6. doi:10.1161/01.CIR.0000070422.41439.04
64. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med.* 2011;365(1):32–43. doi:10.1056/NEJMoa1100171
65. Chen HH, Anstrom KJ, Givertz MM, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA.* 2013;310(23):2533–43. doi:10.1001/jama.2013.282190
66. Massie BM, O'Connor CM, Metra M, et al. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. *N Engl J Med.* 2010;363(15):1419–1428. doi:10.1056/NEJMoa0912613
67. Paterna S, Fasullo S, Parrinello G, et al. Short-term effects of hypertonic saline solution in acute heart failure and long-term effects of a moderate sodium restriction in patients with compensated heart failure with New York Heart Association class III (Class C) (SMAC-HF Study). *Am J Med Sci.* 2011;342(1):27–37. doi:10.1097/MAJ.0b013e31820f10ad
68. Paterna S, Di Pasquale P, Parrinello G, et al. Changes in brain natriuretic peptide levels and bioelectrical impedance measurements after treatment with high-dose furosemide and hypertonic saline solution versus high-dose furosemide alone in refractory congestive heart failure: a double-blind study. *J Am Coll Cardiol.* 2005;45(12):1997–2003. doi:10.1016/j.jacc.2005.01.059
69. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol.* 2007;49(6):675–683. doi:10.1016/j.jacc.2006.07.073
70. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med.* 2012;367:2296–2304. doi:10.1056/NEJMoa1210357
71. Costanzo MR, Negoianu D, Jaski BE, et al. Aquapheresis versus intravenous diuretics and hospitalizations for heart failure. *JACC Heart Fail.* 2016;4(2):95–105. doi:10.1016/j.jchf.2015.08.005
72. Koch M, Haastert B, Kohnle M, et al. Peritoneal dialysis relieves clinical symptoms and is well tolerated in patients with refractory heart failure and chronic kidney disease. *Eur J Heart Fail.* 2012;14(5):530–539. doi:10.1093/eurjhf/hfs035
73. Sarnak MJ, Auguste BL, Brown E, et al. Cardiovascular effects of home dialysis therapies: a scientific statement from the American Heart Association. *Circulation.* 2022;146(11):e146–e164. doi:10.1161/CIR.0000000000001088
74. Molina EJ, Shah P, Kiernan MS, et al. The Society of Thoracic Surgeons Intermacs 2020 annual report. *Ann Thorac Surg.* 2021;111(3):778–792. doi:10.1016/j.athoracsur.2020.12.038
75. Bansal N, Hailpern SM, Katz R, et al. Outcomes associated with left ventricular assist devices among recipients with and without end-stage renal disease. *JAMA Intern Med.* 2018;178(2):204–209. doi:10.1001/jamainternmed.2017.4831
76. Walther CP, Niu J, Winkelmayer WC, et al. Implantable ventricular assist device use and outcomes in people with end-stage renal disease. *J Am Heart Assoc.* 2018;7(14):e008664. doi:10.1161/JAHA.118.008664
77. Brisco MA, Kimmel SE, Coca SG, et al. Prevalence and prognostic importance of changes in renal function after mechanical circulatory support. *Circ Heart Fail.* 2014;7(1):68–75. doi:10.1161/CIRCHEARTFAILURE.113.000507
78. Rodrigues J, Alam A, Giannetti N, Bernard C, Podymow T. Secondary hemosiderosis on kidney biopsy in a patient with a left ventricular assist device. *Am J Med Sci.* 2014;347(2):172–173. doi:10.1097/MAJ.0000000000000221
79. Ootaki C, Yamashita M, Ootaki Y, et al. Reduced pulsatility induces periarteritis in kidney: role of the local renin–angiotensin system. *J Thorac Cardiovasc Surg.* 2008;136(1):150–158. doi:10.1016/j.jtcvs.2007.12.023
80. Roehm B, Vest AR, Weiner DE. Left ventricular assist devices, kidney disease, and dialysis. *Am J Kidney Dis.* 2018;71(2):257–266. doi:10.1053/j.ajkd.2017.09.019
81. Rosenblum H, Kapur NK, Abraham WT, et al. Conceptual considerations for device-based therapy in acute decompensated heart failure: DRI2P2S. *Circ Heart Fail.* 2020;13(4):e006731. doi:10.1161/CIRCHEARTFAILURE.119.006731

Published Online Ahead of Print: January 13, 2023

Downloaded from http://journals.lww.com/cjasn by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 10/16/2024